

NEUROGEN CORP.
1999.04.02 1999-285420; 1999US-127624) (2000.10.12) C07D
2351/4, A61K 31/4045, 31/4184, G01N 33/50, A61P 25/00, C07D 209/14
New N-benzimidazolymethyl and N-indolymethyl benzamide
derivatives, useful as corticotropin releasing factor (CRF)
modulators for treating e.g. depression, anxiety, cardiovascular
and eating disorders (Eng)
C2000-195862 (NAE AL AM AT AU AZ BA BB BG BR BY CA CH
CN CR CU CZ DE DK DM EE ES FI GB GD GE GH
GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK
LR LS LT LU LV MA MD MG MK MN MW MX NO
NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT
TZ UA UG US UZ VU YU ZA ZW) R(At BE CH CY
DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU
MCMW NL OA PT SD SE SL SZ TZ UG ZW)
Addnl. Data: HORVATH R F, GE P, YOON T, HUTCHISON A
2000.03.31 2000WQ-US08570, 1999.04.02 1999US-285420

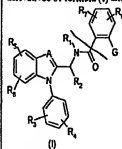
NOVELTY

N-benzimidazolymethyl and N-indolymethyl benzamide
derivatives (I) are new.

H(4-E5, 6-D1, 6-DS, 12-K4F, 14-E11, 14-F1,
14-J1A1, 14-J1B4) .7

DETAILED DESCRIPTION

N-benzimidazolymethyl and N-indolymethyl benzamide
derivatives of formula (I) and their salts are new.



A = N or CY;
Y = H or 1-6C alkyl;
R1 = H, 1-6C alkyl or hydroxy 1-6C alkyl;
R2 = H or 1-6C alkyl, provided R2 is H when A is CY;

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G, R₃, R₄ = H, halo, CF₃, OCF₃, CN, 1-6C alkyl, 1-6C alkoxy, OH,
hydroxy 1-6C alkyl, 1-6C alkoxy 1-6C alkyl, SH, 1-6C
alkylthio, thio 1-6C alkyl or 1-6C alkylthio 1-6C alkyl; and
R₅-R₆ = H, halo, CF₃, OCF₃, CN, 1-6C alkyl, 1-6C alkoxy, OH, SH, 1-
6C alkoxy 1-6C alkoxy, hydroxy 1-6C alkoxy, hydroxy 1-
6C alkyl, 1-6C alkoxy 1-6C alkyl, amino, mono- or
dialkylamino, 1-6C alkylthio, thio 1-6C alkyl or 1-6C
alkylthio 1-6C alkyl.

INDEPENDENT CLAIMS are included for:

- (1) a packaged pharmaceutical composition comprising (I), a container
and instructions;
- (2) a method of localizing CRF receptors in tissue section samples by
contacting the sample with labelled (I) and binding, washing the
sample to remove unbound compound, and detecting the bound
compound; and
- (3) preparation of (I).

ACTIVITY

Tranquilizer; antidepressant; cardiatic; anorectic; anabolic;
nootropic; neuroprotective; antiparkinsonian; anticonvulsant; anti-
HIV; vasotropic; vulnerary; antiaddictive; analgesic.

MECHANISM OF ACTION

CRF receptor modulator.

In a standard assay of CRF binding, the compounds (I) exhibit an IC₅₀
value of less than 1 micro M; preferably less than 100, especially less
than 10 nM (claimed).

USE

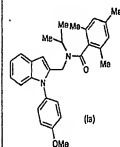
(I) is used to treat stress, anxiety, depression, cardiovascular
disorders, obesity and eating disorders, drug addiction, obsessive-
compulsive disorders, stress, neurological disorders such as
supranuclear palsy, AIDS related dementia, multi infarct dementia,
Alzheimer's disease, Huntington's disease and Parkinson's disease,
ischemia, trauma, fibromyalgia and epilepsy. (I) can also be used as a
probe, for localizing CRF receptors, inhibiting binding of CRF to the
CRF1 receptor in IMR32 cells, and for altering the signal-transducing
activity of a cell surface CRF1 receptor (all claimed).

SPECIFIC COMPOUNDS

68 compounds (I) are specifically claimed, e.g. N-[(1-(4-
methoxyphenyl)indol-2-yl)methyl]-N-(methylethyl)(2,4,6-
trimethylphenyl)carboxamide (Ia).

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ADMINISTRATION

0.1-140 (preferably 0.5-7) mg/kg/day e.g. orally, topically,
parenterally, rectally or by inhalation.

EXAMPLE

(2-aminoethyl)(4-methoxy-2-methylphenyl)amine (60 g) in
chloroform (350 ml) was stirred with imidate (59 g) at room
temperature for one hour. NaHCO₃ (100 ml) was added, and extracted

with dichloromethane (4x150 ml), dried (Na₂SO₄), and the solvent
was removed *in vacuo*. The residue was purified by silica gel
chromatography to give 1-[2-(chloromethyl)benzimidazolyl]-4-
methoxy-2-methylbenzene (IIa) (50 g, 65%). (IIa) (3 g) in acetonitrile
(20 ml) was reacted with isopropylamine (5 ml) at 50°C in a sealed
tube for one hour. Solvent was removed *in vacuo*, and the residue
partitioned between ethyl acetate (30 ml) and 1N NaOH solution (10
ml). The organic layer was dried (Na₂SO₄) to give [(1-(4-methoxy-2-
methylphenyl)benzimidazol-2-yl)methyl](methylethyl)amine (3.1 g,
98%). This amine was stirred with 2,4,6-trimethylbenzoylchloride (2.6
ml) in 1:1 dichloromethane:NaHCO₃ solution (30 ml) for one hour at
room temperature. The mixture was partitioned, the organic layer
dried, and the solvent removed *in vacuo*. The crystallized product was
further dried with ether, filtered and dried to give N-[(1-(4-methoxy-2-
methylphenyl)benzimidazol-2-yl)methyl]-N-(methylethyl)(2,4,6-
trimethylphenyl)carboxamide (Ia) (4.4 g, 92%).

DEFINITIONS

Preferred Definitions :

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(con't)

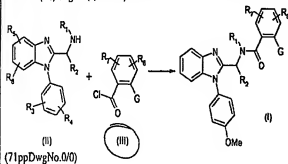
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$R_2 = H$;
 $Q = \text{trimethylphenyl}$;
 $R_3, R_4 = H, F, Cl, OH, CF_3 \text{ or } Me$;
 provided that R_3 and R_4 can not both be H .

TECHNOLOGY FOCUS

Organic Chemistry - Preparation - (I) is prepared by e.g. reacting a benzimidazole compound of formula (II) with a benzoyl chloride of formula (III) to give (I; $A = N$).



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